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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/746,921	12/22/2000	Kevin J. Thorne	2265-15	2764

7590 11/18/2003

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EXAMINER	
PATTEN, PATRICIA A	
ART UNIT	**PAPER NUMBER**
1654	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/746,921	THORNE ET AL.	
	Examiner	Art Unit	
	Patricia A Patten	1654	

-- Th MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *9,11-23,30 and 31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 24-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

RCE Practice

A request for continued examination under 37 CFR § 1.114, including the fee set forth in 37 CFR § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR § 1.114, and the fee set forth in 37 CFR § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR § 1.114. Applicant's submission filed on 10/2/2003 has been entered.

Claims 1-31 are pending in the application.

Claims 9 and 11-23 were withdrawn from consideration as being drawn to a non-elected invention in Paper No. 12.

Election/Restrictions

Newly submitted claims 30 and 31 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 31 is drawn to wherein the composition comprises an acidifying agent and claim 30 is drawn to wherein the composition comprises an additional buffering agent 'other

than a calcium phosphate salt'. The new claims are considered materially different from the originally claimed invention because the original claims did not contain any additional buffering agent or an acidifying agent. Therefore, these claims are patentably distinct from the original claims as they would be classified separately, and would require a separate, burdensome search on the merits.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 30-31 are hereby withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1-8, 10, and 24-29 were examined on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3 and 25-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a substrate, a bone

growth protein, a source of calcium and a source of phosphate which buffers in the acidic region, does not reasonably provide enablement for a composition which provides for the claimed pH ranges (i.e., pH 4 or 5). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 3 and 24-29 all recite wherein the composition buffers the environment to a pH wherein pH 4 and pH 5 are within these ranges.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Inventions targeted for human therapy bear a heavy responsibility to provide supporting evidence because of the unpredictability in biological responses to therapeutic treatments. The standard of enablement is higher for such inventions because effective treatments for disease conditions are relatively rare, and may be unbelievable in the absence of strong supporting evidence. Claims drawn to pharmaceutically acceptable compositions and to methods of administering compounds to humans generally require supporting evidence because of the unpredictability in biological responses to therapeutic treatments.

It is not found in the data presented in Figures 2-8 wherein the pH level of a solution was lowered to between about 4 and 7 (or any of the specific ranges as recited in claims 24-29). As discussed in a previous Office Action, the state of the art is unpredictable. Applicants are stating that their invention performs *a specific function of lowering pH* to between about 4 and about 7 but no evidence of such has been disclosed. There has been no evidence displayed which would indicate any change of pH in solution *in-vitro, in-vivo* or *ex-vivo* after the composition has been introduced. Thus, it is deemed that a composition comprising an acidic calcium phosphate salt may

buffer the immediate surroundings of the composition, however Applicants are *claiming* that the composition will lower the pH to quite acidic pH's such as 4 and 5.

What composition comprising calcium phosphate salts will lower the pH of a solution to the claimed pH ranges? It is known that the pH is dependant upon the volume of the solution, and yet, Applicants have not provided any indication of what compositions will buffer what amount of a solution. As it was previously noted, the only working example present within the Instant specification is performed with Ostite, material characteristics unknown and unexplained by Applicants. As described infra with regard to calcium monophosphate, the most acidic calcium phosphate salt (as known in the art and taught by Applicants) only buffers in a range from about 6.2 to 8.2. Therefore, it is uncertain how to make a composition which buffers in this range without adding an acid to the composition to ensure a pH at these claimed values.

Thus, the dilemma is; how much experimentation would be needed in order to allow the skilled artisan to reproduce the claimed invention? First, the skilled artisan would not know what a 'microenvironment' is, because this term is not defined within the specification. Second, the skilled artisan would not know what composition actually lowers the pH of an unknown volume of solution to the claimed pH ranges. Because of the lack of information regarding making the Instantly claimed compositions, the skilled artisan would need to perform undue experimentation, entailing *rigorous* trial and error protocols in order to determine the exact nature of the composition. This

experimentation would be notably undue considering that the skilled artisan, lacking critical guidance in the Instant specification, *would not have a reasonable expectation of success* because the skilled artisan would need to create a composition which is not fully defined (see rejections under 35 USC 112 second paragraph *supra*), and which buffers an *unknown* amount of surrounding fluid *to a pH of 4 or 5*. The Specification fails to teach specific guidance which would permit the skilled artisan to use the invention commensurate in scope with the claims in that there are no working examples or even suggestions of which compositions actually perform this task and therefore fails to meet the requirements set forth under 35 USC 112 first paragraph.

In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvements while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad

enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8, 10 and 24-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 10 and 24-29 either recite, or depend upon a claim which recites 'microenvironment surrounding said site". The metes and bounds of this phrase are not clearly delineated in that the ordinary artisan would not be able to ascertain what amount of space is at an acid pH. What constitutes a 'microenvironement'? This term is confusing, and it is deemed that the ordinary artisan could not ascertain weather or not they were in possession of the claimed invention upon reading the Instantly recited phrase. Because the Examiner cannot readily determine what Applicants mean by this

phrase, this phrase has been interpreted to mean that the composition donates protons.

Claim Rejections - 35 USC § 102

Claims 1-5, 8 and 10 and 24-27 remain rejected under 35 U.S.C. 102(b) as being anticipated by Ohura et al (1999).

It is noted that claims 3 and 24-27 were examined on the merits for their enabled scope, wherein the composition donates protons to the surface of the bone composition.

Applicants' arguments were fully considered, but not found convincing.

Applicants principally argue that the Examiner has not made a *prima facie* case of inherency: "...it would not be reasonable to conclude that the combination of β-TCP and MCPM in the cement of Ohura et al., or the resulting mixture of mineral salts in the product would necessarily possess an acidic character" (p.7, Arguments). "...It cannot...be assumed that the cement of Ohura et al., or its resulting product mixture, would necessarily cause the implantations site (including the are immediately surrounding the implanted product) to be at an acid pH..or in the specified acid pH range..whereby bone growth would be enhanced compared to other bone growth promoting compositions" (p.7, Arguments). Applicants further argue "Ohura et al. does not teach using MCMP alone as a carrier for BMPs' (p.7, Arguments).

The Examiner respectfully disagrees with these arguments and presents further evidence of inherency:

The Examiner agrees that Ohura et al. does not teach the use of MCMP alone. However, what is known in the art and explained in previous Office Actions is that MCMP is monocalcium monophosphate (a.k.a., monocalcium phosphate, a.k.a. monocalcium phosphate monohydrate), which, as explained by Applicants (i.e., p.13, Instant specification) and which is known in the art, is an *acidic* monophosphate. What is also expressed by Ohuru et al. is that β-TCP and MCMP are not a complex, but individual solids added to the bone matrix; the solubilities of each compound acting independently of each other. It is also known that TCP is very *insoluble*. Further, the pKa of $H_2PO_4^-$ is about 7.2 $X10^{-8}$ ($H_2PO_4^-$ being the ion released after solubilization with water). The reaction is: $H_2PO_4^-$ (aq) ⇌ H^+ (aq) + HPO_4^{2-}. Because phosphoric acid, as well other polyprotic acids, will buffer at about 1 pH unit away from the pKa (in both directions), it is deemed that calcium monophosphate will buffer a solution to between pH 6.2 and pH 8.2. Thus, although Ohura et al. did not explicitly teach wherein the bone composition comprising β-TCP and MCPM would necessarily create an acidic pH, it is deemed that because MCPM is an acidic calcium phosphate which buffers its immediate environment to a pH of 6.2-8.2, and because these ranges fall within the claimed ranges, that the reference anticipates these claims even though

Ohura et al. did not specifically teach these pH ranges (it is noted that a pH below 7 is considered acidic, and that the range of 6.2-8.2 overlaps with the Instantly claimed ranges and therefore anticipates the claims to specific pH ranges). It is further deemed that this buffering would occur until the buffering capacity of the phosphoric acid was reached, *independent on the presence of other species in the bone matrix such as β-TCP* which is, as stated *supra,* highly insoluble and would therefore have little if any buffering capacity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 10 and 28-29 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kwan et al. (US 6,187,047 B1) in view of Constantz (US 5,047,031) for the reasons of record.

Applicants argue that the 'Product is not the same' (p.8, Arguments). Applicants point out that Kwan et al. taught adjustment of the pH of the final mineralized collagen

slurry to 7.5 ± 0.5. It is noted that the premise for this rejection is based upon the obviousness of the invention; namely, that it would have been obvious for one of skill in the art to have combined the ingredients because they are all known for the same purpose. Kwan et al. taught the adjustment of the pH for *storage purposes* and does not change the contention that the combination of ingredients would have been obvious to one of ordinary skill in the art. A combination of the composition taught by Kwan et al. and MCMP would have buffered the surface of the bone matrix to a pH of 6.2-8.2 especially absent convincing evidence to the contrary.

Applicants argue that "...pH plays a strong role in the osteogenic performance of compositions employing bone growth proteins, with 'acidic environments providing dramatically superior results' was unexpected by those of skill in the art at the time of the invention. However, Applicants have not provided for any unexpected results in the Instant specification. On the contrary, the Examiner cannot determine that Applicants have created any unobvious combination of elements. As is seen in the prior art, acidic calcium monophosphate salts such as calcium monophosphates were *well known* in the art to be used in bone compositions. Therefore, the ordinary artisan would have had a reasonable expectation that the combination of elements would have provided for a suitable composition for bone growth. Because calcium phosphate intrinsically contains a phosphoric acid buffering system ($H_2PO_4^-$), it is deemed that calcium phosphate would buffered its immediate environment on the surface of the bone composition thereby

creating an acidic pH *in at least some volume of liquid* prior to the exhaustion of its buffering capacity.

"Notably, there is no teaching or suggestion that the implantable product must be capable of establishing or buffering the pH of the implantation site at one end of that pH range or the other, or anywhere in between" (p. 9, Arguments, referring to Constantz). It is noted that the buffering capacity of brushite (calcium monophosphate) is an intrinsic property of the compound although it is not explicitly stated in the references.

Applicants have not clearly established how their composition differs from the prior art, or why their composition is non-obvious over the combination of the prior art references. In the Instant case, the claimed compositions appear to be the same/obvious over the prior art references for the reasons of record. The ordinary artisan would have had a good expectation that the combination of elements would have provided for a beneficial bone composition. Again, Applicants argue that the Examiner has pointed out that they may have found a new characteristic of an old composition, however, the Specification does not teach otherwise. The only teachings in the specification are drawn to wherein calcium phosphate salts are added to a bone composition. As can be seen *supra*, this was old and known in the art.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A Patten whose telephone number is (703) 308-1189. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (703) 306-3220. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Patricia A Patten
Examiner
Art Unit 1654

11/12/03

PATRICIA PATTEN
PATENT EXAMINER